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STATE OF ISRAEL

זאת לתעודה כי
רצופים בזה העתקים
נכונים של המסמכים
שהופקדו לכתחילה
עם הבקשה לפטנט
לפי הפרטים הרשומים
בעמוד הראשון של
הנספח.

This is to certify that
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PRIORITY DOCUMENT

This 19-02-1998 היום

מ. לפרי
ממונה על הבוחנים

רשם הפטנטים
Registrar of Patents

חוק הפטנטים, תשכ"ז - 1967
PATENTS LAW, 5727-1967

בקשה לפטנט
Application For Patent

לשימוש הלשכה
For Office Use

מספר: 120005
Number

תאריך: 14 -01- 1997
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אני, (שם המבקש, מענו ולגבי גוף מאוגד - מקום התאגדותו)
I, (Name and address of applicant, and in case of body corporate-place of incorporation)

רמות רשות אוניברסיטאית למחקר שמושי ולפיתוח תעשייתי בע"מ, חברה ישראלית, מרח' חיים לבנון 32, רמת-אביב, 69975, ישראל
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The inventors: Arieh SOLOMON
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(בעברית) (Hebrew)
תכשירים רוקחיים לטיפול בעין

(באנגלית) (English)
Pharmaceutical compositions for the treatment of the eye

מבקש בזאת כי ינתן לי עליה פטנט
hereby apply for a patent to be granted to me in respect thereof.

* בקשת חלוקה – Application of Division	* בקשת פטנט מוסף – Appl. for Patent of Addition	* דרישת דין קדימה Priority Claim		
מבקשת פטנט from application	* לבקשה/לפטנט to Patent/Appl.	מספר/סימן Number/Mark	תאריך Date	מדינת האיגוד Convention Country
No. מס'	No. מס'			
dated מיום	dated מיום			

P.O.A. : * יפוי כח : עוד יוגש

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REINHOLD COHN AND PARTNERS
By : –

היום 13 בחודש January שנת 1997
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תכשירים רוקחיים לטיפול בעין

Pharmaceutical compositions for the treatment of the eye

Ramot University Authority for Applied Research & Industrial Development Ltd.

רמות רשות אוניברסיטאית למחקר שמושי ולפיתוח תעשייתי בע"מ

The inventors:

הממציאים:

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PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF THE EYE

FIELD OF THE INVENTION

The present invention concerns pharmaceutical compositions for the treatment of the eyes and more specifically for the treatment of disorders of the anterior segment of the eye.

BACKGROUND OF THE INVENTION

The protective structures of the anterior surface of the eye include the eyelids, conjunctiva, and the cornea. The posterior surfaces of the lids are covered with a mucous membrane, the palpebral conjunctiva, which reflects onto the eye to become the bulbar conjunctiva. The bulbar conjunctival epithelium is continuous with the corneal epithelium which accounts for about 10% of the anterior surface of the eye and is where most of the stationary refraction occurs.

The corneal epithelium is 4–5 cells thick and the superficial cells contain many microvilli. These aid in maintaining the moisture of the epithelial surface by promoting the adhesion of the tear film to the surface. This film lubricates the anterior surface of the eye to decrease the frictional forces arising from the persistent blinking movements of the eyelids, foreign particles on the surface of the eye, and the rational movements of the eyeball. The tear film also transfers oxygen from ambient air to the cornea.

The anterior surface of the eye is vulnerable to damages inflicted by various causes which include: mechanical abrasion of the cornea; contact lens wearing; spontaneous peeling of the epithelium; damage epithelium and stroma in photo-refractive keratectomy; chemical burns; over exposure to ultraviolet light including sunlight; systemic diseases such as Sjogren syndrome, Steven-Johnson syndrome, Cicatricial pemphigoid syndrome; chronic edema of cornea with recurrent erosion of epithelium; impaired tear film formation, and conditions following damage of epithelia due to radial keratotomy.

Aging often causes disorders resulting from slow regeneration of the epithelium. Impaired regeneration and abnormality of cells leads to a decrease in thickness of the epithelial layer and of its adherence to the basal lamina thus decreasing the ability of the cornea to retain the tear film and leading further to epithelial damage.

Following injury to the corneal epithelium, the nearby cells retract slightly, round up and begin an ameboid migration from the basal layer across the exposed basement membrane to cover the defect with a new monolayer of cells. These cells then take on the characteristics of a new basal layer and undergo mitosis to gradually fill in the defect with the full complement of four to five layers of cells. Present treatment for corneal wounds involve applying eye drops to the surface in order to protect the delicate healing wound process from erosion due to blinking and the other sources of friction. There are no currently used medicaments that promote the healing process itself. Attempts to administer fibronectin in order to promote healing of persistent defects of the corneal epithelium failed (Fukuda *et al., Am J. Ophthalmol.*, 119(3):281-287, (1995)).

It would have been highly desirable to provide an ophthalmic composition capable of protecting the corneal epithelium and enhancing healing and regeneration of eye epithelia.

The rate of cell proliferation in many cell types has been correlated with the rate of cholesterol synthesis, more specifically, the biosynthesis of various intermediates of the cholesterol biosynthesis pathway

and their by-products such as Farnesylated proteins and others are involved in the control of cell proliferation. Thus, inhibition of an early enzyme in the biosynthesis of cholesterol inhibits cell growth in cultured fibroblasts (McGuire *et al., J. Biol. Chem.*, 268:22227-22230, (1993)). Factors which cause cholesterol efflux from cells (e.g. high density lipoproteins, HDL) alleviate the negative feedback inhibition of cholesterol synthesis and enhance growth of MDCK cells *in vitro* (Gospodarowicz *et al., J. Cell. Physiol.*, 117:76-90, (1983)).

The cornea is an avascular organ obtaining nutrition from the limbus vasculature by a diffusion process. The epithelium at the outer surface of the cornea is essentially isolated from plasma's large complexes such as HDL which hardly diffuse through the cornea. Thus, HDL which performs the *"reverse cholesterol transport"* from peripheral organs to the liver (Glomset, J.A., *J. Lipid Res.*, 9:155-167, 1968) is not able to perform this task in the corneal epithelium.

SUMMARY OF THE INVENTION

The present invention is based on the surprising finding that high density lipoprotein (HDL), or a combination of its non-cholesterol lipid constituents (phospholipids, and other lipids such as triglycerides, glycerol), which are capable of forming reconstituted HDL, promote normal healing and regeneration of damaged eye epithelium.

Both HDL and said lipid constituents were able to initiate the process of healing, to increase its rate, and to promote reversion of the damaged epithelium of the eye to the normal state, i.e. where the damaged area is covered again by layers of epithelial cells.

Thus, the present invention concerns a pharmaceutical composition for the treatment of disorders of the anterior segment of the eye comprising as an active ingredient, at least one agent capable of causing a net efflux of cholesterol from cells, together with an opthalgestically acceptable carrier.

The term *"treatment"* refers to curing of the disorder of the eye, to alleviation of some of the undesired syndromes of various eye disorders, and/or to prevention of various eye disorders before they are manifested.

The term *"anterior segment of the eye"* refers to the corneal and conjunctival epithelium and includes the epithelial cells, as well as the glands present in the epithelium.

The term *"disorders of the anterior segment of the eye"* refers to disorders which cause physical damage to the corneal or conjunctival epithelium, to disorders which decrease the rate of regeneration of cells making up this epithelium, or to disorders causing diminished secretions from glands present in the conjunctival epithelium, or to a combination of some of these disorders.

Typical disorders of the anterior segment of the eye caused by physical or chemical damage are: mechanical abrasion of the cornea, corneal epithelial defects created by wearing contact lens, corneal epithelial defects created by spontaneous peeling of the epithelium, corneal damage following photo–reactive keratectomy, injuries caused by chemical substances, damage caused by exposure to ultraviolet light, systemic diseases creating damage to the corneal epithelium and conjunctiva, for example, Sjorgren–Syndrome, Steven–Johnson Syndrome, Cicatricial Pemphigoid Syndrome, chronic edema of the cornea with recurrent erosion of epithelium and the like.

Typical disorders of the anterior segment of the eye caused by decrease in the rate of generation of cells is deterioration of the eye due to old age or due to anti–proliferative treatment.

Typical disorders of the anterior segment of the eye caused by diminished secretion are dry eye and tear film disfunction which are due to old age, various diseases or are caused as a side effect of systemic medication.

The pharmaceutical composition of the present invention may be administered to persons suffering from disorders which causes damage to the corneal or conjunctiva epithelia, or in conjunction with treatments which are

known to cause such damage, for example, laser or radial keratectomy or administration of various systemic or topical medications.

The pharmaceutical compounds of the invention, due to their amphoteric nature, are also capable of substituting the natural tear film and serving as lubricants, and thus, beyond their effect in the promotion of healing of the damaged eye epithelium, are also capable of relieving the syndrome of dry eye, which may be the cause of the physical damage of the epithelium, may be a result of the physical damage of the epithelium, or may be the sole disorder affecting the person's eye. Where the pharmaceutical composition is intended, *inter alia*, to treat dry eye, it should also include water/saline and a viscous substance such as an ophthalmologically acceptable polysaccharide in order to mimic as closely as possible the constitutes of the natural tears.

The active agents of the invention are those capable of causing a net efflux of cholesterol from cells. Locating candidate agents capable of generating a net cholesterol efflux, may be carried out by determining the net efflux of labeled cholesterol from cells according to the method described in Naphtali Savion and Shlomo Kotev-Emeth, *Eur. J. Biochem.*, 183:363-370 (1989). Briefly, confluent endothelial and smooth muscle cultures are cultured in dishes and incorporate H^3-cholesterol by exposure to H^3-cholesterol labeled serum. The candidate which is to be tested as an effector of a net efflux of cholesterol is then added to the cell culture and the percentage of radioactivity that remains after incubation with the tested compound for 24 hrs. is determined. Candidates which are able to significantly lower the amount of label cholesterol in these cells, are those which are capable of serving as active agents in the pharmaceutical compositions of the invention.

Preferably, the present invention concerns a pharmaceutical composition for the treatment of disorders of the anterior segment of the eye comprising as an active agent at least one compound selected from the group consisting of:

i. high density lipoprotein (HDL);

ii. phospholipids and/or spingolipids;

iii. a composition of matter comprising phospholipids and at least one other lipid component of HDL other than cholesterol and cholesteryl-ester; and

iv. at least one HDL Apolipoprotein.

The term *"high density lipoprotein"* refers to lipoproteins which may be isolated from humans or other mammalian sources (e.g. bovine plasma), for example, as specified in Denis Gospodarowicz *"Methods for Preparation of Media, Supplements, and Substrata for Serum-Free Animal Cell Culture"*, pp. 69-86, 1984, Alan R. Liss, Inc., New York, New York or other isolation methods based on the density of the HDL.

The term *"phospholipids"*, refers to phospholipids which naturally occur in HDL such as phosphatidylcholine, phosphatidylserine and phosphatidylinositol. An example of *"sphingolipids"* also is sphingomyelin.

The term *"and at least one other lipid component of HDL other than cholesterol and cholesteryl-ester"* refers to glycerides such as glycerol and to triglycerides. In accordance with the invention glycerides and triglycerides which are not present naturally in HDL, but have an analogous function to glycerides and triglycerides present in HDL may also be used. The composition of matter comprising the non-cholesterol non-cholesteryl-ester lipid components of HDL, which are generally phospholipids, triglycerides and glycerides, is capable of forming together what is termed as *"reconstituted HDL"* (Gillote *et al., J. Biol. Chem.*, 271:23792-23798, 1996). This term refers to a complex comprising phospholipids, triglycerides and glycerides, which differs from natural HDL by lack of cholesterol and cholesteryl-esters, as well as by the lack of the apolipoprotein. Reconstituted HDL particles are prepared by the chelate dispersion/Bio-Bead removal technique (Sparks *et al., J. Biol. Chem.* 267:25830-25838, 1992) Typically, compounds which are used in intravenous nutrition as a source of essential fatty acids, are suitable for serving as the lipid compo-

nents of HDL. Example being Intralipid™, (Pharmacia AB, Sweden), Lipofundin™ (Braun Melsungen AG, Germany) and others.

The term *"HDL apolipoproteins"* refers to typically apolipoprotein A–I, A–IV and E–apolipo–proteins or a combination thereof, either isolated from a natural human or mammalian source (Savion and Gamliel, *Arterio–sclerosis*, 8:178–186, 1988). Apolipoprotein–E is purified according to Wernette–Hammond *et al., J. Biol. Chem.*, 264:9094–9101, 1989. The HDL apolipoproteins may also be prepared by various genetic engineering methods described in Breslow, *et al., Proc. Natl. Acad. Sci.*, 79:6861–6865, 1982, for example: Human Apolipoprotein A–I gene can be prepared according to the method of Karathanasis *et al., Proc. Natl. Acad. Sci.*, 80:6147–6151, 1983; Human Apolipoprotein A–IV gene according to Elshourbagy, *et al., J. Biol. Chem.*, 262:7973–7981, 1987; and Human Apolipoprotein E gene according to Das, *et al., J. Biol. Chem.*, 260: 6240–6247, 1985; Paik, *et al., Proc. Natl. Acad. Sci.*, 82:3445–3449, 1985.

The composition of the present invention may further comprise albumin.

Albumin is the most abundant plasma protein and serves as the plasma carrier of free fatty acids. Each albumin molecule has 27 binding sites for fatty acids. Albumin may thus serve as a scavenger for toxic free fatty acids released by the damaged anterior chamber tissue upon its inclusion in the reconstituted HDL.

The pharmaceutical compositions of the invention, may further comprise other ingredients having ophthalgesic affects, especially those which are known to facilitate healing and regeneration of cornea and conjunctiva such as growth factors, for example, keratinocyte growth factor (KGF/FGF7), or epidermal growth factor (EGF) and other growth factors of the EGF family known in the art; various attachment factors such as laminin or fibronectin, and extracellular matrix components such as collagen, heparan sulfate proteoglycans and others.

The pharmaceutical compositions of the invention may also include agents capable of ultraviolet light protection, such as oxybenzone 3%, and other such preparations known in the art.

The pharmaceutical compositions of the invention should be administered in the form of eye drops or eye salves together with opthalgestically acceptable carriers. The composition may be in the form of an emulsion, micelles liposomes, etc. The concentration of the active ingredients in the composition should be in the range of 0.1–20%, preferably 0.2–10%, most preferably 0.2–2%.

Some disorders of the eye, which are to be treated by the pharmaceutical compositions of the invention manifest diminished liquid clearance from the eye causing water retention which eventually leads to explosion of eye membranes. In such cases, it is preferable that the compositions of the invention are present in a hyperosmotic formulation which can serve to help draw excess liquid from the eye. Such hyperosmotic formulation may be formed, for example, by addition of NaCl to the composition.

By another aspect, the present invention concerns a storage preparation for storing and maintaining isolated corneas, for example, in an eye bank. In order to maintain the viability of epithelial cells as well as the exposed endothelium of the eye, it is preferable to add to the storage medium an effective amount of at least one agent capable of causing a net efflux of cholesterol from cells, as explained above.

The invention now will be illustrated with reference to some non limiting drawings and examples.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows fluorescein staining of untreated damaged eye cornea 5 days after surgery (x 16);

Fig. 2 shows fluorescein staining of untreated damaged eye cornea 12 days after surgery (x 16);

Fig. 3A shows histological staining of normal cornea;

Fig. 3B shows the histological staining of untreated damaged eye cornea 12 days after surgery;

Fig. 4 shows fluorescein staining of damaged eye cornea following Intralipid™ treatment;

Fig. 5 shows histological staining of damaged eye cornea following Lyteers™ treatment;

Fig. 6 shows fluorescein staining of damaged eye cornea after 3 days of treatment with HDL;

Fig. 7 shows fluorescein staining of damaged eye cornea at the end of treatment with HDL; and

Fig. 8 shows the histological staining of damaged eye cornea after HDL treatment.

DETAILED DESCRIPTION OF THE INVENTION

I. Experimental Procedures

A. Animal model of corneal epithelium and conjunctival epithelium damage

The rabbit model for keratoconjunctivitis (Gilbard *et al., J. Inv. Ophthal. Vis. Sci.*, 2:225-228 (1987)) was used with slight modification. Surgery performed on anesthetized rabbits using surgical microscope (Inami, Japan) using surgical microscope (involved excision of the plical fold over the eye, occlusion of the lacrimal duct, and peeling of the palpebral and bulbar conjunctiva. This surgery was done on one eye of 20 rabbits of average age 3 months of both sexes. Surgery and all subsequent treatments was done in accordance with ARVO rules for animal care in research. However, tear film osmolarity is elevated by postoperative day 1. Corneal epithelial glycogen levels decline progressively, and conjunctival goblet cell density decreases. These pathologies lead to corneal epithelium damage which covers the entire corneal surface by the fifth postoperative day, and it was at this time that treatment of the eyes commenced.

B. HDL preparation

HDL was prepared from human plasma by differential ultracentrifugation flotation (*Havel et al.*, "Distribution and chemical composition of ultracentrifugally lipoproteins in human serum", *J. Clin. Invest.*, 34:1345-53, (1995)).

C. Clinical evaluation

Corneal lesions were clinically evaluated by biomicroscopy with slit lamp (Haag Streit, Switzerland) with cobalt filter illumination following the fluorescein staining of the corneas. Photography of the fluorescein staining was taken by slit lamp mounted camera (Topcon, Japan). At the end of each experiment, the rabbits were sacrificed and the cornea excised at paraformaldehyde and examined for epithelial lesions.

D. Histological examination

At the end of the treatment the rabbits were sacrificed by intravenous injection of pentobarbitone in a lethal dose. The eyes were enuclated and fixated in 4% paraformaldehyde solution. The sections of the eye were embedded in parafin blocks and microtom sections were stained with hematoxylin eosine for light microscope examination.

II. Treatment of corneal epithelium damage caused by conjunctival epithelium damage

Example 1

Rabbits with cornea damage induced as above were treated as follows: Five rabbits were treated with commercially available artificial tears (Lyteers™), five rabbits were treated with HDL (1mg protein/ml) in phosphate buffered saline, five rabbits were treated with a commercially available lipid mixture (10% Intralipid™: 10% soybean oil, 1.2% egg phospholipids, 2.2% glycerol), and two rabbits were left untreated. Treatment consisted of applying two drops to the eye 3 times a day for

seven consecutive days. The eyes were evaluated clinically during the experiment and pictures taken every other day of fluorescein stained corneas.

Fluorescein staining of damaged eye taken 5 and 12 days following surgery were shown in Figs. 1 and 2, respectively. As can be seen, the surface of the untreated eye becomes progressively more scratched and opaque, as time progresses, leading eventually to blurring of vision.

Histological staining of damaged eye is shown in Fig. 3B and is compared to histological staining of normal eye 3A. As can be seen, in the damaged eye there was complete erosion of the epithelium in the exposed area of the eye due to constant rubbing of the epithelium by the lids as well as severe keratitis and vascularization of the cornea.

Animal eyes which were treated with Intralipid™ show complete reversal to normal morphological structure as indicated by fluorescein staining (Fig. 4). Histological examination of animals' eyes treated with Lyteer™, (Fig. 5) which is commercial artifical tears composed mainly of water and a viscous substance, did not show reversion to normal epithelium. Contrary to normal eyes, the damaged area was not covered again by normal layers of cubid epithelial cells having a single top layer of wing cells, but was covered instead only by a single layer of wing cells showing complete lack of cubid cells. These results indicate that artificial tears cannot promote regeneration of normal eye epithelium.

Contrary to this, animal eyes treated with HDL showed essentially a complete reversion to normal morphological structure as indicated by fluorescein staining taken at the third day (Fig. 6) and at the end of treatment with HDL (Fig. 7) as well as by histological staining (Fig. 8). Histological staining which show essentially complete reversion back to normal of the eye epithelium characterized by formation of several layers of cubid cells and a single top layer of wing cells.

These results clearly indicate that both HDL and Intralipid™ were able to promote healing and regeneration of damaged eye epithelium and reversion back to normal epithelium.

CLAIMS:

1. A pharmaceutical composition for the treatment of disorders of the anterior segment of the eye comprising as an active ingredient, at least one agent capable of causing a net efflux of cholesterol from cells, together with an ophthagestically acceptable carrier.

2. A pharmaceutical composition according to Claim 1, wherein the anterior segment of the eye is the corneal epithelium and stromal conjunctiva, and the glands present in them.

3. A pharmaceutical composition according to Claim 1, wherein the disorders are manifested by physical and chemical damage to the conjunctival and corneal epithelium.

4. A pharmaceutical composition according to Claim 3, wherein the disorders are selected from the group consisting of: mechanical abrasion of the cornea; corneal epithelial defects created by contact lens wearing; corneal epithelial defects created by spontaneous peeling of the epithelium; corneal damage following photo-refractive keratectomy; injuries caused by chemical substances; injuries caused by ultraviolet light exposure; systemic diseases causing damage to the corneal epithelium and conjunctiva; chronic edema of cornea with recurrent erosion of epithelium; and conditions following damage of epithelia due to radial keratotomy.

5. A pharmaceutical composition according to Claim 1, wherein the disorders include a decrease of secretion from glands located in the conjunctiva.

6. A pharmaceutical composition according to Claim 5, wherein the disorders are selected from the group consisting of: dry eye and tear film disfunction caused by medication.

7. A pharmaceutical composition according to Claim 1, wherein the disorders are manifested by a slow rate of regeneration of cells of the anterior segment of the eye.

8. A pharmaceutical composition according to Claim 7, wherein the slow rate of regeneration is caused by old age, or by administration of anti-proliferative substances.

9. A pharmaceutical composition according to Claims 1 to 8, wherein said agent is one or more of the group consisting of:

i. high density lipoprotein (HDL);

ii. phospholipids and/or sphingolipids;

iii. a composition of matter comprising phospholipids and at least one other lipid component of HDL other than cholesterol and cholestryl-ester; and

iv. at least one HDL Apolipoprotein.

10. A pharmaceutical composition according to Claim 9, further comprising albumin.

11. A pharmaceutical composition according to Claim 9, wherein the HDL is human or bovine HDL.

12. A pharmaceutical composition according to Claim 9, wherein the phospholipids are selected from the group consisting of: phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinosital.

13. A pharmaceutical composition according to Claim 9, wherein the sphingolipids are sphingomyelins.

14. A pharmaceutical composition according to Claim 9, wherein the other lipid components of HDL are triglycerides and/or glycerol.

15. A pharmaceutical composition according to Claim 9, wherein the apolipoprotein is selected from the group consisting of: Apolipoprotein A-I, Apolipoprotein A-IV and Apolipoprotein E or a combination of one or more apolipoproteins.

16. A pharmaceutical composition according to Claims 1 to 15, further comprising a growth factor, an attachment factor or an extracellular component.

17. A pharmaceutical composition according to Claim 16, wherein the growth factor is selected from the group consisting of: Keratinocyte Growth

Factor (KGF/FGF7), Epidermal Growth Factor (EGF) and other growth factors of the FGF family.

18. A pharmaceutical composition according to Claim 16, wherein the attachment factor is selected from the group consisting of: laminin and fibronectin.

19. A pharmaceutical composition according to Claim 16, wherein the extracellular matrix components are selected from the group consisting of: collagen and heparan sulfate proteoglycans.

20. A pharmaceutical composition according to any one of Claims 1 to 19 further comprising an agent capable of protection from U.V. radiation.

21. A pharmaceutical composition according to Claim 20, wherein the agent capable of protecting from U.V. radiation is oxybenzone.

22. A storage medium for the preservation of isolated cornea comprising at least one agent capable of causing net efflux of cholesterol from cells.

23. A storage medium according to Claim 22, wherein the agent capable of causing a net efflux of cholesterol from cells is one or more of the group consisting of:

i. high density lipoprotein (HDL);

ii. phospholipids and/or sphingolipids;

iii. a composition of matter comprising phospholipids and at least one other lipid component of HDL other than cholesterol and cholestryl–ester; and

iv. at least one HDL Apolipoprotein.

24. A storage medium according to Claim 23, further comprising albumin.

25. A storage medium according to Claim 23, wherein the HDL is human or bovine HDL.

26. A storage medium according to Claim 23, wherein the phospho–lipids are selected from the group consisting of: phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinosital.

27. A storage medium according to Claim 23, wherein the sphingolipids are sphingomyelin.

28. A storage medium according to Claim 23, wherein the other lipid components of HDL are triglycerides and/or glycerol.

29. A storage medium according to Claim 23, wherein the apolipoprotein is selected from the group consisting of Apolipoprotein A-I, Apolipoprotein A-IV and Apolipoprotein E or a combination of one or more apolipoproteins.

For the Applicants,
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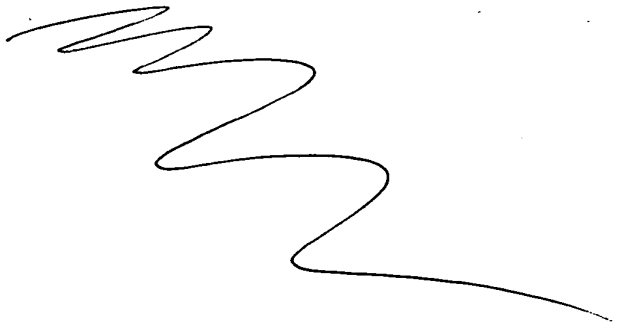
By:



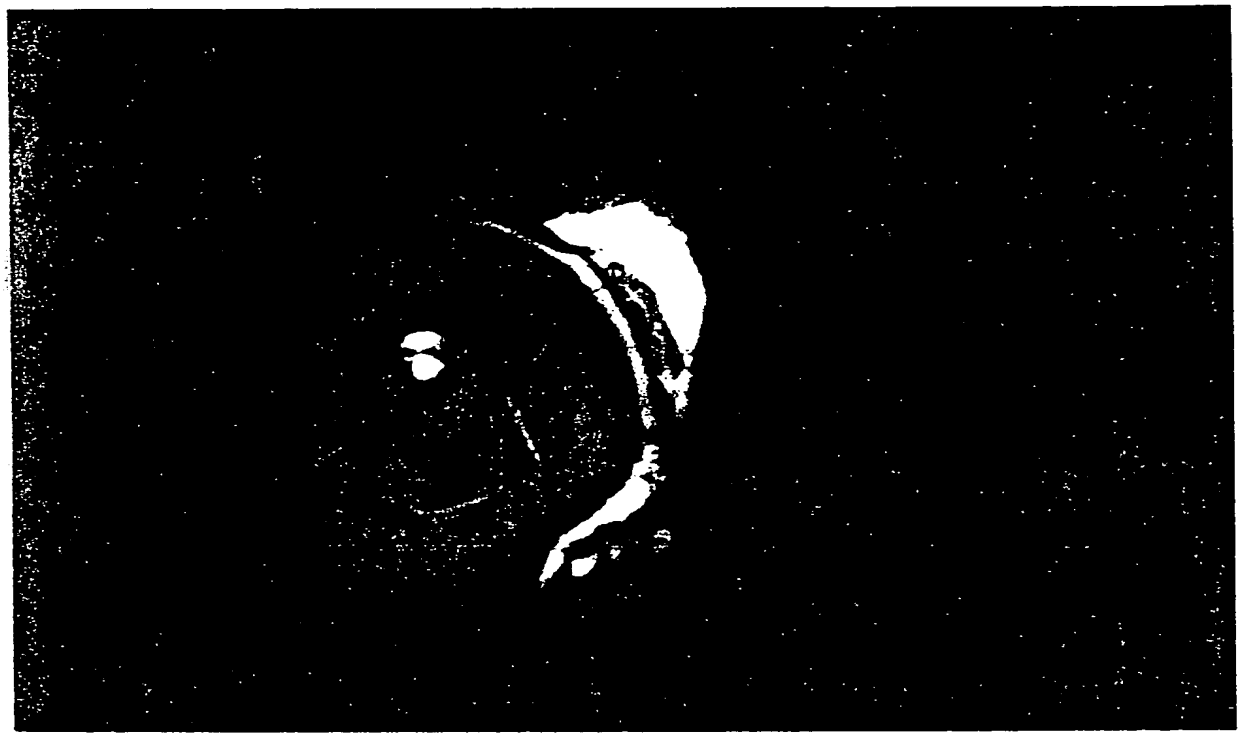


FIG. 1

FIG. 2

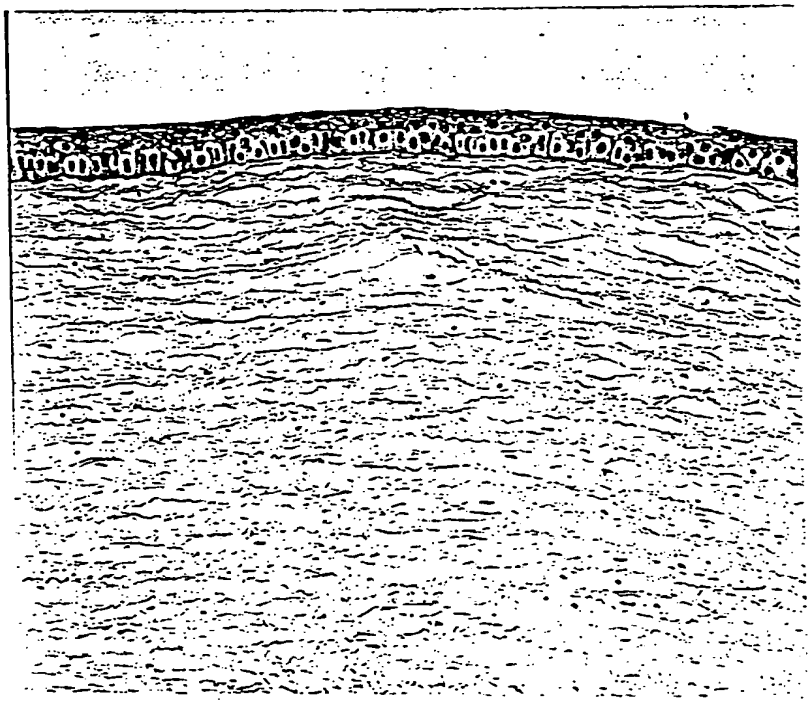


FIG. 3A

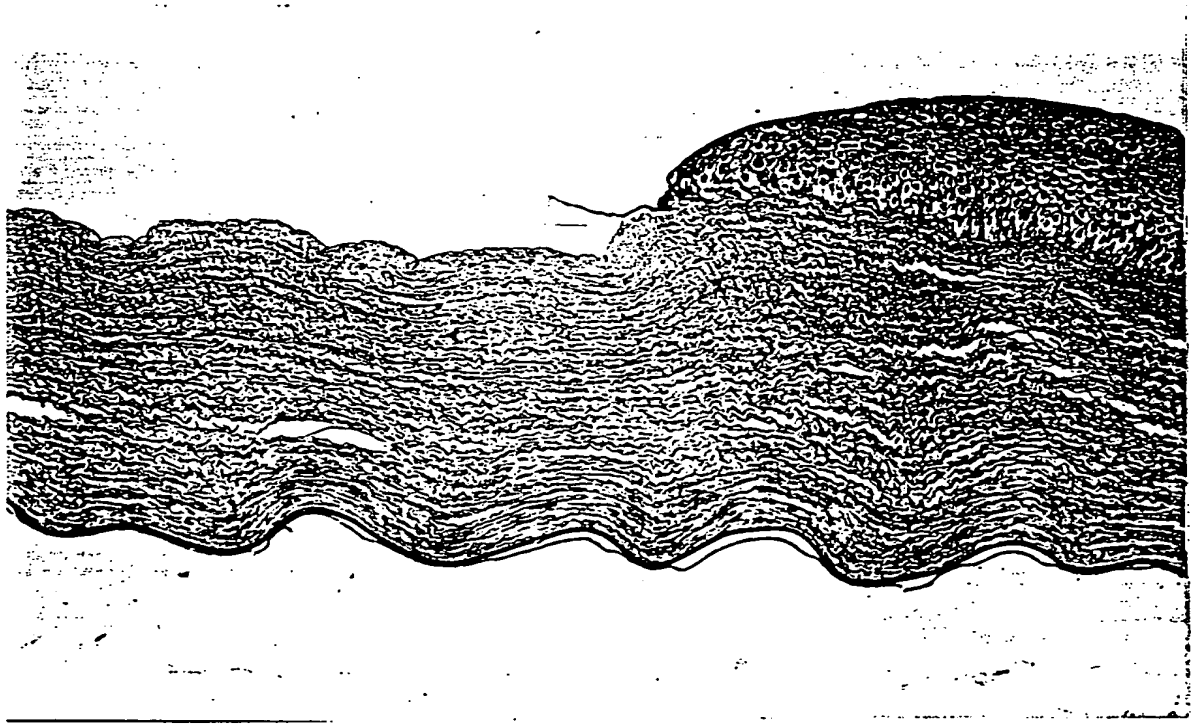


FIG. 3B

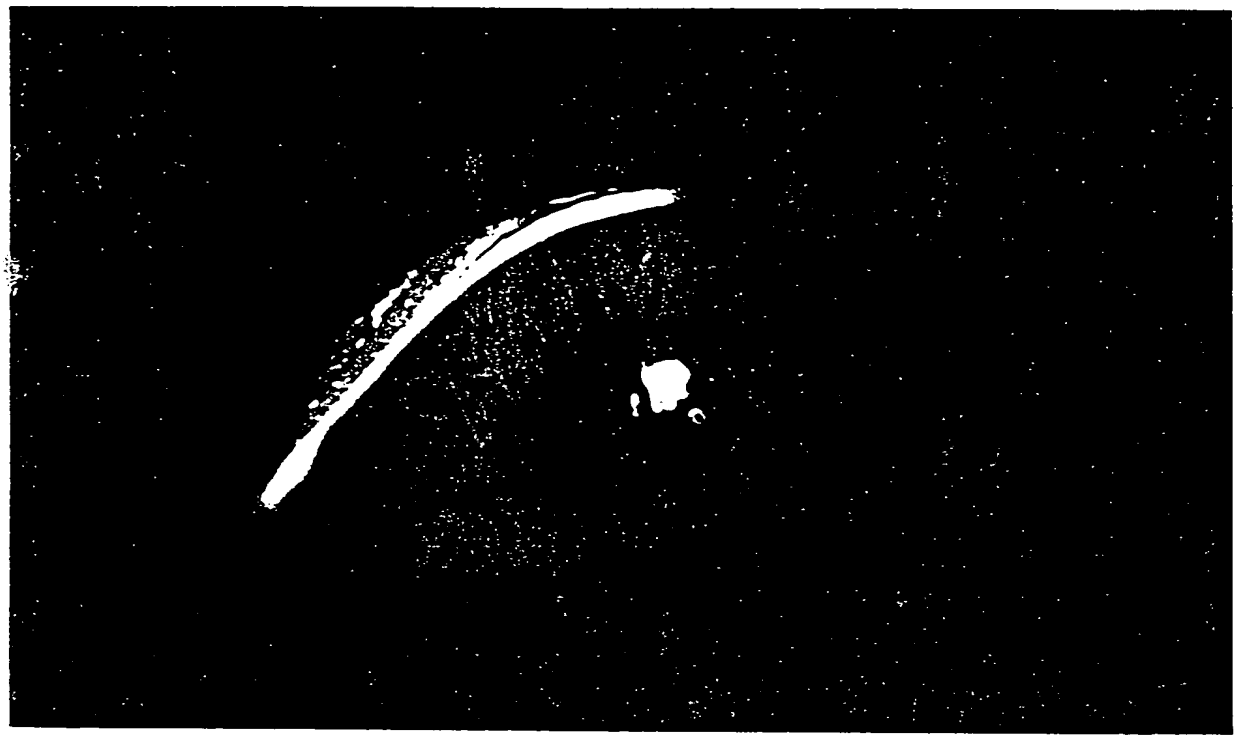


FIG. 4

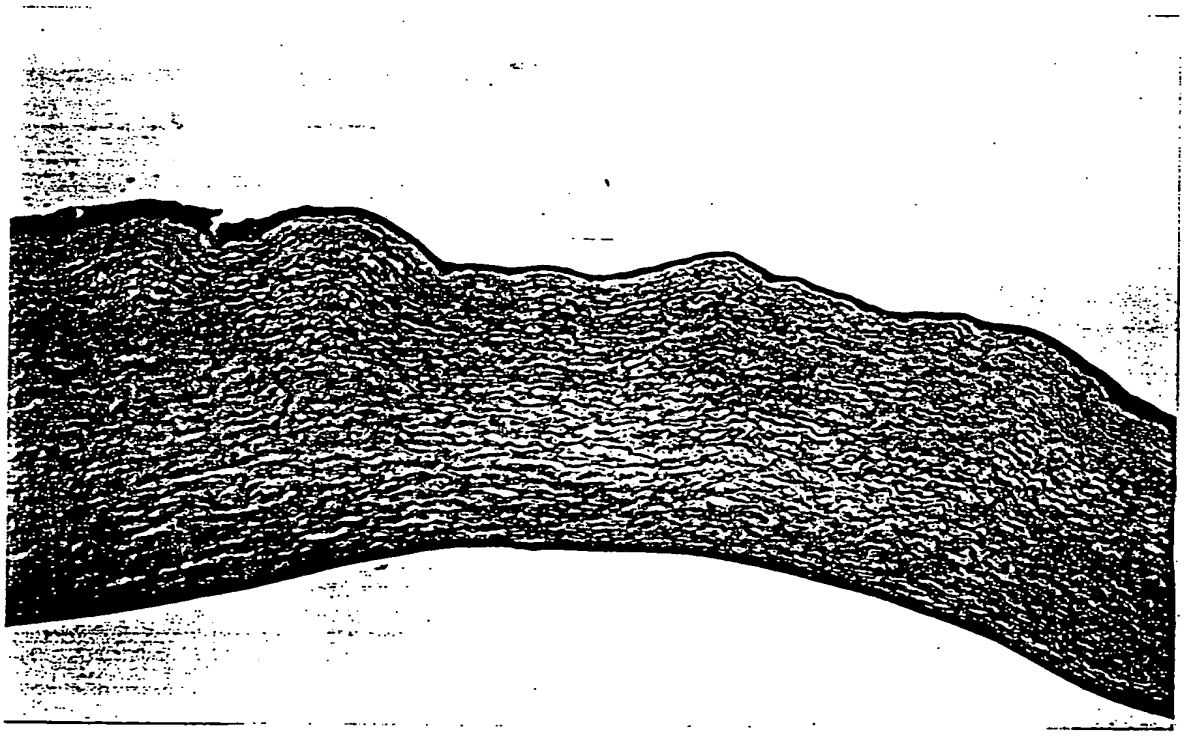


FIG. 5

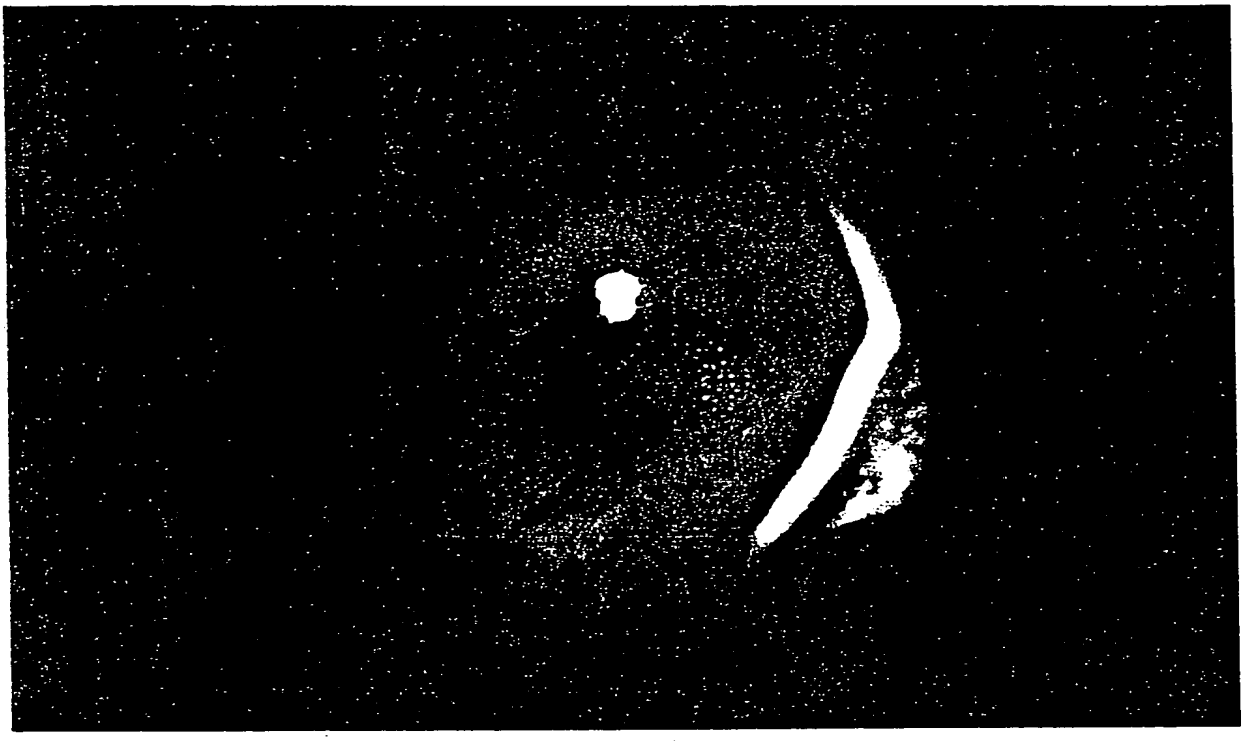


FIG. 6

FIG. 7

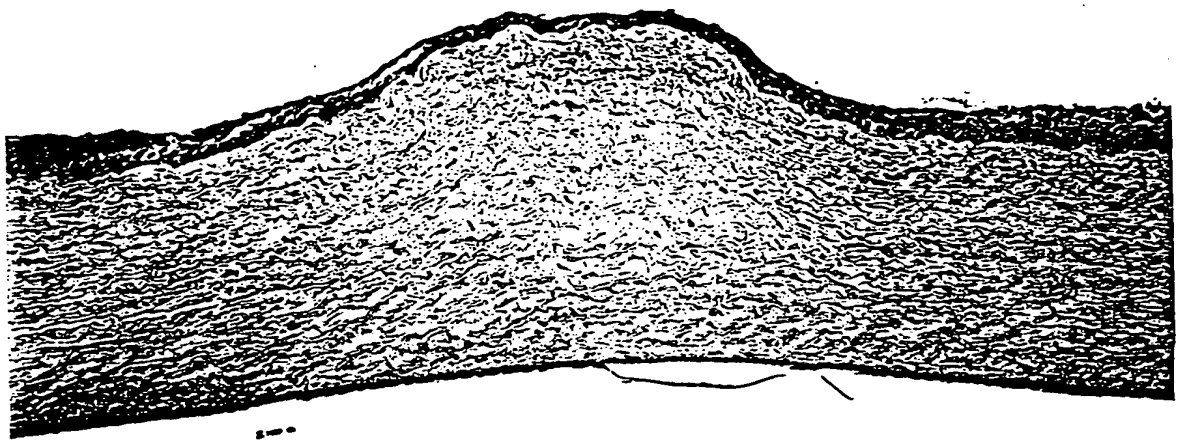


FIG. 8